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Access to Cancer Precision Medicines in Switzerland: A Comparative Analysis (USA and EU) and Health Policy Implications

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Abstracts
Social health insurance is mandatory in Switzerland and covers the costs of basic medical care. In general, with regard to medicines, the costs are only reimbursed if the drug is (1) approved by Swissmedic and (2) listed on the so-called Spezialitätenliste (SL) by the Federal Office of Public Health (FOPH). However, the SL does not include all drugs. For non-SL drugs, cost coverage is only granted under exceptional circumstances. Absence of cost coverage by social health insurance is especially problematic for patients who need access to cancer drugs, since they are often costly. Even if such cancer drugs are approved by Swissmedic, patients may still lack access to them. Therefore, access to medicines includes two aspects: (1) the availability of a drug on the market (i.e., approval of a drug) and (2) inclusion on the SL (i.e., cost coverage by social health insurance). In this study, we aim to compare the current approval regulations for oncologic precision medicines in the USA, Europe, and Switzerland; to investigate cost coverage for these drugs in Switzerland; and to develop health policy implications about how access to these drugs could be improved in Switzerland.

Introduction

Over a hundred new cancer drugs have been approved by Swissmedic, the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA), and over 38,000 cancer drug trials have been initiated since 2000. A shift can be observed from the development of classic chemotherapeutic drugs to immunotherapies and biomarker-defined cancer drugs, also known as precision medicines or precision drugs [1, 2].

At the same time, health costs are rising continuously. In 2016, the total health costs in Switzerland amounted to more than CHF 80 billion, which is an increase of 3.7% compared to 2015 [3]. Expenditures on pharmaceutical drugs contribute to this increase. In 2013, they amounted

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to USD 666 per capita, which is approximately 30% above the OECD average [4]. This expenditure increased to USD 982 in 2016 [5]. A major reason for this great increase lies in certain high-cost drugs, such as oncology drugs. In 2016, the costs of cancer drugs amounted to CHF 500 million [5].

Social health insurance is mandatory in Switzerland and covers the costs of basic medical care. In general, it only covers the costs of medicines that are (1) approved by Swissmedic and (2) listed on the so-called Spezialitätenliste (SL) by the Federal Office of Public Health (FOPH). The FOPH decides whether a specific drug should be included on the SL, and if so, determines the maximum price in negotiation with the manufacturer. However, the SL does not include all drugs. For non-SL drugs, cost coverage is only granted under exceptional circumstances. Absence of cost coverage is often problematic for patients since cancer drugs can be very costly. Therefore, even if such cancer drugs are approved by Swissmedic, patients may still lack access to them. In sum, access to medicines includes two aspects: (1) the availability of a drug on the market (i.e., approval of a drug) and (2) cost coverage by social health insurance.

In this study, we aim (a) to compare the current approval regulations for oncologic precision medicines in the USA, Europe, and Switzerland; (b) to investigate cost coverage for these drugs in Switzerland; and (c) to assess health policy implications about how access to these drugs could be improved in Switzerland.

Opportunities and Challenges of Precision Medicine

The general concept of personalized medicine is decades old [6]. However, the mapping of the human genome, completed in 2003, increased the volume of available genetic data and raised the expectation that gene-based drugs would enable new and promising approaches to successful treatment, especially in oncology [7, 8]. The project led to an increased understanding of the molecular pathways that underlie cancer [9]. The term *precision medicine* can be understood as targeted diagnosis and therapy, i.e., an approach that takes individual variability – particularly genetic variation – into account when developing medical treatments [10]. Some precision medicines have become standards of care, e.g., trastuzumab for HER2-positive breast cancer or vemurafenib for melanomas that express mutated BRAF (Table 1) [10–12].

Table 1. Examples of precision medicines in oncology

Drug	Molecular target	Treatment (initial indication)
Xalkori (crizotinib)	ALK+	Non-small cell lung cancer after progression on first-line therapy
Zykadia (ceritinib)	ALK+	Non-small cell lung cancer for patients resistant or intolerant to treatment with crizotinib
Herceptin (trastuzumab)	HER2+	Breast cancer
Perjeta (pertuzumab)	HER2+	Breast cancer

Precision drugs are supposed to offer a greater clinical benefit or reduced side effects to the targeted patient populations [13]. However, targeting a specific mutation – and, therefore, a smaller patient population – may also result in smaller clinical trial sizes and an increased use of surrogate endpoints in clinical trials [2]. A study showed that precision medicines approved by the FDA in 2013–2017 were based on fewer pivotal trials that were less likely to be randomized, blinded, or controlled with either an active or a placebo comparator [2]. For example, the pivotal trials for the approval of crizotinib (Xalkori) in 2011 by the FDA were based on two single-arm studies with surrogate efficacy endpoints (objective response rate) and fewer than 140 patients in each trial [14].

Precision medicines are regularly associated with high costs. For example, ibritumomab tiuxetan (Zevalin), a monoclonal antibody radioimmunotherapy, costs CHF 23,520 (factory price) per infusion in Switzerland, and the costs of the chimeric antigen receptor T-cell therapy tisagenlecleucel (Kymriah) are USD 470,000 in the USA and EUR 320,000 in Germany. This anticancer drug is already approved in Switzerland by Swissmedic, but the FOPH did not yet set the price. Most likely, it will also be high in Switzerland. Novartis expects a price of CHF 370,000 [15]. Nonetheless, advocates of precision medicines emphasize the lower treatment costs overall [13]. However, various cost-effectiveness studies have demonstrated the opposite. For example, in an individual-based intervention study by the public health services of Norway, a single-agent biomarker-based approach was 2.5 times more expensive than best supportive care [13, 16]. Furthermore, for most patients with metastatic cancer, the duration of benefit is limited, and is followed by drug resistance and cancer progression [9].

Table 2. Accelerated programs in the USA, the EU, and Switzerland

FDA		EMA		Swissmedic	
Program name	Eligibility	Program name	Eligibility	Program name	Eligibility
Orphan Drug Designation	Drug treats disease occurring in <200,000 people per year in the USA, or in more than 200,000 people but for which there are no reasonable expectations that the drug development costs will be recovered	Orphan Drug Designation	Drug must be intended for treatment, prevention, or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development; and no satisfactory method of diagnosis, prevention, or treatment of the condition concerned can be authorized, or, if such methods exist, the drug must be of significant benefit to those affected by the condition	"Wichtiges Arzneimittel für seltene Krankheiten" (orphan drug designation)	1. Drug treats life-threatening or severely debilitating disease, and disease occurs in max. 5/10,000 people in Switzerland; or 2. Drug has been designated in another country by a comparable approval agency as an important drug for orphan diseases
Fast Track	1. Drug treats life-threatening or severely debilitating diseases, and nonclinical or clinical data demonstrate the potential to address unmet medical needs; or 2. Drug is designated as a qualified infectious disease product	PRIME	Drug of major interest for public health, in particular from the viewpoint of therapeutic innovation (unmet medical needs)	"Vereinfachte Zulassung" (simplified authorization procedure)	1. Drugs with known active pharmaceutical ingredients; or 2. Complementary drugs; or 3. Drugs prepared for stocks by a public pharmacy, a drugstore, or another establishment holding a manufacturing license; or 4. Drugs prepared by a hospital pharmacy or in the hospital's own radiopharmaceutical unit for the needs of the hospital; or 5. Drugs prepared by the army and used in the context of the coordinated army medical corps; or 6. Important drugs for rare diseases
Priority Review	1. Drug treats serious condition and, if approved, would provide a significant improvement in safety or effectiveness; or 2. Any supplement that proposes a labeling change pursuant to a report on a pediatric study; or 3. An application for a drug that has been designated as a qualified infectious disease product; or 4. Any application or supplement for a drug submitted with a priority review voucher	Accelerated Assessment	Drugs of major interest for public health, in particular from the viewpoint of therapeutic innovation (unmet medical needs)		
Accelerated Approval	Drug intended to treat a serious condition; generally provides a meaningful advantage over available therapies; and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit	Conditional Marketing Approval	Drug for seriously debilitating or life-threatening disease, including orphan drugs, fulfilling the following criteria: positive risk-benefit balance; applicant likely to be able to provide comprehensive data after authorization; drug fulfils unmet medical needs; benefits of immediate availability outweigh risks due to additional data still being required	"Befristete Zulassung" (conditional approval)	Drug treats life-threatening or disabling disease; approval in accordance with human health; high clinical benefit is expected; and no approved alternative drug is available in Switzerland
Breakthrough Therapy	1. Drug intended to treat a serious condition, and nonclinical or clinical data demonstrate its potential to address unmet medical needs; or 2. Drug is designated as a qualified infectious disease product				

Approval for Precision Medicines in the USA, EU, and Switzerland

In general, before a drug can be sold widely in a country, it must have been approved by a national agency. In the USA, approval is being granted by the FDA, in the EU by the EMA, and in Switzerland by Swissmedic. The agencies must determine, based on the data they receive, whether a drug is of high quality, is safe, and has the effect it is meant to have based on adequate and well-controlled investigations (such as randomized controlled trials assessing validated clinical outcomes) [17]. The agencies make these determinations by reviewing the results of these clinical studies by – or on behalf of – the manufacturer [17]. The approval process can be time-consuming (e.g., in the USA, the FDA must review the data within a 10-month window) and may delay access to medicines for patients. This can be especially problematic for patients with serious or life-threatening conditions who have no other treatment options [17]. In response, regulators and legislators in the USA, the EU, and Switzerland created different programs or designations to expedite approval for promising new drugs intended for unmet medical needs (Table 2). These programs are not congru-

ent between jurisdictions; however, they have similarities, and eligibility criteria regularly overlap. Depending on the program, among other things, the assessment time for marketing authorization is shorter, a drug can be (conditionally) authorized on the basis of less complete clinical data, or more guidance on drug development is being granted [2, 17].

All three jurisdictions implemented the so-called orphan drug designation (Table 2). In 2016 alone, orphan designation was sought for 568 products in the USA. Six of the top 10 by revenue were designated as orphan drugs for oncology diagnoses, with annual sales ranging from USD 1.1 billion to 4.4 billion [18, 19]. Furthermore, studies analyzing drugs approved between 2002 and 2015 have shown that approximately 40–45% of all orphan drug designations are requested for rare cancers [20, 21]. The number of biomarker-derived cancer drugs that are being designated orphan status is yearly increasing as well [20]. These high revenues achieved with drugs that, in fact, are not used for treating true orphan diseases are in conflict with regulators' aims in the different jurisdictions [22]. Unfortunately, only little information on these approval data is publicly available in Switzerland. Therefore, it may only be assumed that the patterns observed in the USA apply to Switzerland as well.

Cost Coverage for Precision Medicines and Fundamental Rights in Switzerland

Fundamental rights are rights recognized and supported by the government that are retained by each individual, such as the right to life, prohibition of the death penalty, prohibition of discrimination, or the right to privacy [23].

Based on the non-discrimination principle in Art. 8 para. 2 Cst., all patients must have, among other things, equal access to medicines [24], i.e., patients suffering from orphan diseases must have equal access to drugs compared to patients who are diagnosed with non-orphan diseases. However, in general, manufacturers have a greater incentive to develop drugs for diseases that affect larger populations to maximize their profits. Therefore, the government developed expedited pathways, as outlined in Table 2, to incentivize, among other things, the development of orphan drugs and fulfil the requirements of the non-discrimination principle [25].

Additionally, a fundamental right relevant to access to medicines is Art. 12 Cst., which states that persons in need and unable to provide for themselves have the right to assistance and care, and to the financial means required for a decent standard of living. Based on this provision, the question arises whether there is a fundamental right to access to health and medicine in Switzerland. The majority of Swiss legal scholars denies this and does not recognize access to medicine as a fundamental right [24, 25]. Moreover, the scope of application of Art. 12 Cst. is limited to emergency situations, i.e., minimal survival support [26–28]. However, even though the Swiss constitution does not comprise a fundamental right to medicine, Art. 41 Cst. contains the social objectives that must be addressed by the Swiss Confederation and the cantons. Among other things, the Swiss constitution gives the government the mandate to ensure that there is sufficient high-quality basic medical care available to all [29]. One major tool for fulfilling this objective is everyone's responsibility to be insured with a social health insurance agency. This agency covers the costs of basic medical care if a specific medical procedure, including the prescription of drugs, is expedient, has a clinical benefit, and is economical (i.e., has a good cost-benefit ratio) [24].

In general, the cost of a drug is covered by the social health insurance agency if it is (1) approved by Swissmedic and (2) listed on the SL. The FOPH only adds a drug to the SL if it fulfills the basic requirements outlined above (expediency, clinical benefit, and economy). However, not all cancer drugs are on the SL. Drugs that are not considered having a clinical benefit or a good cost-benefit ratio, or are not considered basic medical care, will not be included on the list.

Nonetheless, under specific circumstances, the social health insurance agency is legally required to cover the costs of an approved non-SL drug if (a) use of the drug is an indispensable prerequisite for the performance of another medical service covered by the social health insurance agency or (b) use of the drug is expected to provide a *significant therapeutic benefit* against a disease that is *fatal* to the insured patient or may result in *severe and chronic* adverse health effects, and no other effective and approved treatment is available due to a *lack of therapeutic alternatives* [30, 31]. With regard to cancer drugs, the second condition (b) is relevant. In an application for cost coverage ("Kostengutsprache") to the patient's social health insurance agency, it is the responsibility of the patient to prove that, in this specific case, the abovementioned prerequisites are met. In practice, such applications for cost coverage in most cases are written by the treating physician. The social health insurance agency then decides whether the prerequisites for covering the costs are fulfilled.

In oncology, the most challenging prerequisite to prove is that of a *significant therapeutic benefit*. The term is ambiguous and there is no clear understanding of what it actually means. A further challenge is that social health insurance agencies have considerable discretionary power when deciding on whether or not the prerequisites for cost coverage are met. Additionally, cost coverage in these individual cases strongly depends on the quality of the application for cost coverage, and therefore on the qualifications and efforts of the physician in charge. Due to these circumstances, it is possible that some patients get cost coverage from one social health insurance agency, while other patients are not granted cost coverage by (other) social health insurance agencies [32]. This contains an element of arbitrariness and is unfortunate considering patients' fundamental rights – and also considering that the number of non-SL precision drugs in oncology may increase in the near future if manufacturers are going to have (increasingly) high price expectations and negotiations with the FOPH will not succeed. It is essential that, as a rule, the costs of (precision cancer) drugs with a clinical benefit are covered by social health insurance agencies, and that cost coverage via Art. 71a et seq. KVV will only apply in exceptional cases.

Conclusion and Implications

Precision medicines in oncology enable promising approaches to successful treatment. Only drugs that offer high clinical benefit and address unmet medical needs should be approved through expedited regulatory approval, which includes, among other things, shorter review times and fewer clinical trials. More and more, precision medicines are approved through expedited pathways in the USA, and it may be assumed that this is also true for Switzerland. Therefore, the exception increasingly becomes the rule. Applying expedited regulatory approval in circumstances where the precondition of a great clinical benefit is not met wastes resources that might otherwise have been used for drugs with high clinical benefit.

To facilitate research in this field, and thereby improve the validity of its implications, detailed information about the drug approval and health technology assessment process in Switzerland should be publicly available. Furthermore, the increasing health care costs raise questions regarding cost coverage. It is essential that the pricing of drugs is based on their clinical value and that drugs with a clinical benefit are prioritized for listing on the SL. Moreover, the application and decision-making process regarding cost coverage for drugs not listed on the SL should be standardized to minimize access inequality and comply with the Swiss fundamental rights.

Statement of Ethics

The guidelines for human studies were not applicable to our study.

Disclosure Statement

The authors declare no conflicts of interest.

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Author Contributions

K.N.V.: study concept and design, drafting of the manuscript, supervision, and guarantor; U.J.M. and T.J.R.: critical revision of the manuscript.

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